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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/28, 9/52, 31/44 | A1

(11) International Publication Number: **WO 98/40054**

(43) International Publication Date: 17 September 1998 (17.09.98)

(21) International Application Number: PCT/SE98/00356

(22) International Filing Date: 27 February 1998 (27.02.98)

(30) Priority Data:
9700885-8 12 March 1997 (12.03.97) SE

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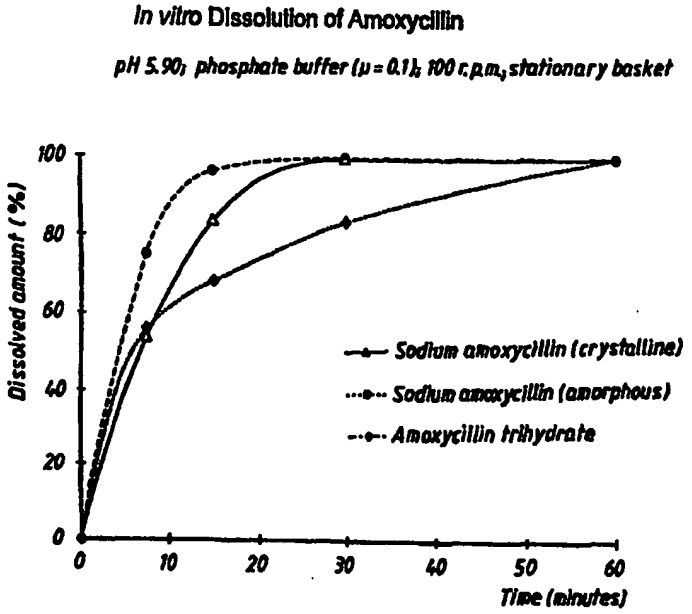
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AN ENTERIC COATED ORAL DOSAGE FORM COMPRISING SODIUM AMOXYCILLIN



(57) Abstract

An enteric coated oral dosage form comprising sodium amoxycillin, wherein the dosage form is a single unit tableted dosage form or a multiple unit tableted dosage form is claimed. Processes for the manufacture of the dosage forms as well as the formulations, use in the treatment of *Helicobacter pylori* infections are claimed.

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AN ENTERIC COATED ORAL DOSAGE FORM COMPRISING SODIUM AMOXYCILLIN

Field of the Invention

This invention relates to new formulations of sodium amoxycillin, in particular enteric coated oral dosage formulations of sodium amoxycillin, processes for their manufacture and their use in the treatment of *Helicobacter pylori* infections.

Background of the Invention

The relationship between gastrointestinal disorders and infections and *Helicobacter pylori* (*H. pylori*) was first proposed in 1983 by Warren in The Lancet (1983) **1**, 1273. A clear link has now been established.

Recently a panel convened by the US National Institute of Health (NIH) has recommended complete eradication of *H. pylori* for those patients with peptic ulcer diseases who are infected with the bacterium. Therapies which have been proposed in this regard include combinations of antibacterial compounds; combinations of a bismuth compound and antibacterial compounds (see for example International Patent Application WO 89/03219); combinations of ranitidine and antibacterial compounds; and combinations of proton pump inhibitors with antibacterial compounds (see for example International Patent Applications WO 93/21920 and WO 92/03135).

In these proposed combination therapies each single active substance is administered separately in different dosage forms. However, administration of two or more different tablets is not typically seen as convenient or satisfactory by the patient and therefore such therapy has the disadvantage of poor patient compliance and therefore poor results.

Thus, in order to limit the problem of poor patient compliance in the treatment of *H. pylori* infections, there is a need for an effective single dosage unit comprising two or more of the above active ingredients.

In the treatment of *H. pylori* infections with antibacterial agents acting via the systemic circulation - whether this is in combination with one or more of the above active agents or otherwise - it is desirable to ensure that release of active substance(s) takes place in the small intestines where the systemic circulation is known to occur. This is because the topical effects of antibacterial agents on *H. pylori* are known to be limited when compared to systemic circulation. See R.J. Adamek et al, Am. J. Gastroenterol., 88 (5), (1993), 792-793. Accordingly, it is desirable to produce the highest possible concentration of antibacterial agent in the serum in order to eradicate infection.

The antibacterial agent amoxycillin has been known for many years to be useful in the treatment of wide variety of infections, ranging from bronchitis to urinary-tract infections.

In the treatment of peptic ulcer patients infected with the *H. pylori*, amoxycillin has been indicated as being a preferred antibacterial agent. For example, combination therapies comprising coadministration of omeprazole and amoxycillin have been approved by regulatory authorities in e.g. the United Kingdom and Sweden.

Amoxycillin is typically administered in two forms, amoxycillin trihydrate which is typically administered orally and sodium amoxycillin which is typically administered by injection. Thus, a tablet formulation typically comprises amoxycillin trihydrate and the injection is a solution of sodium amoxicyllin.

Although oral formulations of sodium amoxycillin have been reported (see e.g. International Patent Application WO 94/00112), at present none are presently commercially available.

Enteric coated formulations comprising sodium amoxycillin are not previously known at the knowledge of the Applicant.

We have found that, in the treatment of *H. pylori* infections, the above problems may be solved by providing an enteric coated formulation of sodium amoxycillin which may be used as a single therapy or in a combination therapy.

Brief Description of the Invention

According to the invention there are provided enteric coated oral dosage forms comprising sodium amoxycillin (hereinafter referred to as "the dosage forms according to the invention").

Enteric coatings are well known in the art of drug formulation as an effective method of preventing the release of pharmaceutically active agents in the stomach, but which will dissolve and release drug in the small intestine. They are typically used to prevent the release of drugs which are inactivated by the stomach's contents (e.g. pancreatin and erythromycin) or which irritate the gastric mucosa (e.g. aspirin, i.e. acetyl salicylic acid).

We have found that sodium amoxycillin exhibits a surprisingly high dissolution rate at pH values typically experienced in the small intestine when compared to amoxycillin trihydrate and that the dosage forms according to the invention comprising exhibit significantly higher maximum serum concentrations. Thus enhanced eradication of *H. pylori*, when compared with conventional formulations of amoxycillin trihydrate, are experienced with an enteric coated formulation of sodium amoxycillin.

The present invention relates to an enteric coated oral dosage form providing a fast release of sodium amoxicillin after passage of the stomach and thus a high plasma concentration of amoxicillin and which dosage form in combination with a proton pump inhibitor provides an enhanced eradication of *H. pylori*.

Brief Desription of Drawings

Figure 1 shows the result of *in vitro* dissolution test of tablets.

Detailed Description of the Invention

The dosage forms according to the invention may be formulated as a single unit or as a multiple unit tableted dosage form.

Unless otherwise stated or indicated the term "single unit" denotes that the tablet matrix contains the active substance homogenously distributed beneath the surface area and the term "multiple unit" denotes that the active substance is present in the tablet in several units (of which each one may have its own protective surface layer). In both cases the tablet may contain either one single active substance or one or more additional active substances.

When the dosage form according to the invention is a single unit, sodium amoxycillin may be formulated as a solid granulation along with inactive excipients and compressed into a single unit tablet, prior to application of the enteric coating.

Examples of inactive excipients which may be used include diluents, binders, lubricants and, if necessary, wetting agents.

Examples of suitable diluents include lactose, sucrose, dextrose, starches (e.g. sodium starch glycolate, corn starch) cellulose derivatives (e.g. low substituted hydroxypropyl cellulose, microcrystalline cellulose), mannitol, crosslinked polyvinyl pyrrolidone, microcrystalline and colloidal anhydrous silicon dioxide (Aerosil®).

The dry mixture of sodium amoxycillin may subsequently be mixed with a binder, for example polyvinyl pyrrolidone, hydroxypropyl cellulose, sorbitol and gelatin.

Suitable lubricants which may be employed for the tableting process include for example sodium stearyl fumarate, magnesium stearate and talc.

Suitable wetting agents include for instance sodium lauryl sulphate dissolved in distilled water.

Sodium amoxycillin may be dry mixed with the appropriate excipients and then tableted, or the mixture may be wet massed with a granulation liquid. The wet mass is dried, preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for tableting. The tablets are enteric coated in a suitable equipment.

When the dosage form according to the invention is a tableted multiple unit dosage form, the enteric coated pellets, or granules, comprising sodium amoxycillin are prepared as hereinbefore described for tablets. The enteric coated pellets are mixed with tablet excipients such as fillers, binders, disintegrants and lubricants, and the dry mixture is then compressed into a multiple unit tableted dosage form.

In order to improve the stability of certain dosage forms according to the invention, the solid tableted granulation or the prepared pellets may optionally be coated with at least one separating layer before application of the enteric coating.

Examples of materials which may be used as a separating layer include pharmaceutically acceptable compounds such as sugar, polyethylene glycol, polyvinylpyrrolidine, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium, water soluble salts of enteric coating polymers or mixtures thereof.

The separating layer may further comprise additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as magnesium stearate, titanium dioxide, talc or mixtures thereof.

Separating layers may be applied to the prepared tablets or pellets by coating or layering procedures in suitable equipment, such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layers may be applied to the tablets or pellets by using a powder coating technique.

The separating layer, when applied, may be of a variable thickness. The maximum thickness of the separating layer is normally only limited by processing conditions.

The separating layer may further serve as a diffusion barrier and may act as a pH-buffering zone. The pH-buffering properties of the separating layer may be further strengthened by introducing into the layer one or more substances chosen from a group of compounds often used in antacid formulations, for example magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds (e.g. $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$ or $MgO.Al_2O_3.2SiO_2.nH_2O$), aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak , inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other compounds may be added to increase the thickness of the layer and thereby strengthen the diffusion barrier.

The separating layer may alternatively be formed *in situ*, for example by reaction of an enteric coating polymer layer with an alkaline reacting compound contained in the tablets or pellets, upon application of the enteric coating onto the tablets or pellets.

Enteric coatings which may be employed include those known to those skilled in the art, for example cellulose acetate phthalate, acrylate polymers (e.g. acrylic resins such as Eudragit L and Eudragit S), hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid copolymers, hydroxypropyl methylcellulose acetate succinate,

polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or combinations thereof.

The enteric coating layers may also contain appropriate quantities of pharmaceutically acceptable plasticizers in order to obtain the desired mechanical properties (e.g. flexibility and hardness). Suitable plasticizers include triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or combinations thereof.

The amount of plasticizer will depend upon the nature of the constituents of the enteric coating layer formula and how much of the said formula is to be applied to the pellets. Ideally the mechanical properties should be adjusted so that the acid resistance of the enteric coated pellets does not significantly alter during compression of pellets into tablets. Typical amounts of plasticizer are above 10% by weight of the enteric coating layer polymer(s), preferably 15 - 50% and more preferably 20 - 50%.

Further additives which may be employed in the enteric coating layer include dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate or -methylmethacrylate), anti-tacking and anti-foaming agents. Other compounds may be added to increase film thickness of the enteric coating layer.

The film thickness of the enteric coating layer is preferably at least 10 μm, preferably more than 20 μm.

Enteric coated pellets may be coated further with one or more over-coating layers in order to prevent agglomeration of pellets and to protect the enteric coating layer from cracking during the compaction process, i.e. the compression of the pellets into a tablet.

The over-coating layers may be applied to the enteric coated pellets by coating or layering procedures using suitable equipment such as a coating pan, a coating granulator or in a fluidized bed apparatus, using water and/or organic solvents for the coating or layering process.

Suitable materials for use as the over-coating layers include sugar, polyethylene glycol, polyvinylpyrrolidine, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium or combinations thereof.

The overcoating layer may further comprise additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included in the over-coating layer. The maximum thickness of the applied over-coating layer(s) is normally only limited by processing conditions.

The prepared single unit tablet or compressed multiple unit tablet is optionally covered with at least one film-forming agent in order that the tablets obtains a smooth surface and to further enhance the stability of the tablets during packaging and transport. Such a tablet coating layer may further comprise additives such as anti-tacking agents, colorants and pigments.

According to further aspects of the invention there are provided processes for the manufacture of a single unit or a multiple unit dosage form according to the invention.

The dosage forms according to the invention are especially advantageous in the treatment of *H. pylori* infections. They are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and depends upon various factors including the individual requirements of the patient, the mode of administration and the disease state to be treated. In general each dosage form will comprise an amount of sodium amoxycillin corresponding to 50 mg to 2.0 g, preferably 100 mg to 1.0 g amoxycillin.

According to a further aspect of the invention there is provided the use of sodium amoxycillin in the manufacture of an enteric coated oral dosage form for use in the treatment of *H. pylori* infections.

The dosage forms according to the invention may be administered alone or in combination with proton pump inhibitors. Any compound which is known in the art and indicated as being a proton pump inhibitor may be used in conjunction with the dosage forms according to the invention. Proton pump inhibitors may be used in any form (e.g. in the none-salt form or as an alkali or an alkaline earth metal salt). Examples of suitable proton pump inhibitors include those described in European Patent Applications EP 0 005 129, EP 1 174 726 and EP 1 166 287; United Kingdom Patent Application GB 2 163 747; and International Patent Applications WO 90/06925, WO 94/27988 and WO 95/01977. Particular proton pump inhibitors which may be mentioned include omeprazole, lansoprazole, pantoprazole, pariprazole (rabeprazole) and limoprazole or its single enantiomers. Of particular interest is omeprazole, S-omeprazole or an alkaline salt thereof.

Proton pump inhibitors may be coadministered separately along with the dosage forms according to the invention. However, in order to eliminate the problems of poor patient compliance mentioned hereinbefore we prefer that the dosage form further comprises a proton pump inhibitor, i.e. that the sodium amoxycillin and proton pump inhibitor are coformulated in an enteric coated oral dosage form.

Coformulation of proton pump inhibitors and sodium amoxycillin into an enteric coated oral dosage form may be carried out in accordance with known techniques, such as those described hereinbefore and/or those described in International Patent Application WO 96/01623.

Alternatively the dosage forms according to the invention may be administered in combination with another gastric acid suppressing agents, such as a H_2-receptor antagonist, for instance ranitidine, cimetidine or famotidine.

The dosage forms according to the invention may further be administered in combination with other antibacterial agents. Antibacterial agents which may be mentioned include for example nitroimidazole antibiotics, tetracyclines, penicillins, cephalosporins, carbopenems, aminoglycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. Examples of antibacterial compounds are: ampicillin, amoxicillin trihydrate, benzylpenicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, cyclacillin, dicloxacillin, methicillin, oxacillin, peperacillin, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetrame, cefixime, cefoxitin, ceftazidime, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalexin, cefaclor, cedadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, erythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, tinidazole, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, oflaxacin, temafloxacin, doxycycline, minocycline, tetracycline, chlortetracycline, oxytetracycline, methacycline, rolitetracyclin, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazide, sulfadiazin, sulfametoxazol, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquine, chlorhexidine, dichlorobenzylalcohol, methyl-2-pentylphenol.

The dosage forms according to the invention have the advantage that they are especially advantageous in the treatment of *H. pylori* infections, for example as shown in the tests described below.

The dosage forms according to the invention may also have the advantage that they are less toxic than, are more easily prepared than, produce less side effects than, have a longer shelf-life than, increase the stability of the pharmaceutically active compound more than, or have other useful pharmacological properties over, similar dosage forms which are known in the prior art.

Tests

Test A

In vitro Dissolution

Discs having a diameter of 11.3 mm were compressed of different substances in a Diaf excenter press using flat faced table punches. The discs were centrically mounted on a round steel plate with hollow fitting for the discs. The discs were attached to the steel plate using a water resistant tape with a circular hole of 0.50 cm^2. The steel plate and the disc were attached to a motor (IKA RW20 DZM). While rotating, the disc was lowered into 200 ml of buffer pH 5.9 thermostated at 37°C. The rotating velocity was 500 rpm. At each run, the dissolution medium was analysed by continuous recirculation through the spectrophotometer using a 10 mm flow cuvette and a peristaltic pump.

Concentrations in the dissolution medium were determined spetrophotometrically using a Perkin Elmer Lambda 2 spectrophotometer. The pH values were measured using a Metrohm 620 pH-meter.

The observed dissolution rates, G, measured as $(mg)/(cm^2 . s)$ were calculated by linear regression analysis of the amount of drug dissolved per cm^2 as a function of time.

Test B

Urea breath test or Urease biopsy test were used to show activity for *Helicobacter pylori.*

The invention is illustrated, but in no way limited, by the following examples.

Examples

Example 1: Dissolution test of tablets

The *in vitro* dissolution (Test A) of sodium amoxycillin (lyophilised), sodium amoxycillin (crystalline) and amoxycillin trihydrate was determined in a buffer solution at pH 5.9 (NaH_2PO_4 and Na_2HPO_4; ionic strength = 0.1 μ).

The dissolution rates from centrically mounted discs prepared from the different substances, as desribed in Test A, are shown in Figure 1. The dissolved amounts were normalized to 100% dissolution after 60 minutes.

The dissolution rate of amoxycillin sodium is 100 times faster than for amoxycillin trihydrate. No difference of the dissolution rate between lyophilised and crystalline amoxycillin sodium was observed.

Example 2: Preparation of enteric coated tablets comprising sodium amoxycillin

Sodium amoxycillin 224 g
corresponds to 200 g amoxycillin
Microcrystalline cellulose 245 g
Sodium starch glycolate 75 g
Polyvinylpyrrolidone 38 g
Magnesium stearate 8.4 g

Sodium amoxycillin was mixed in a planetary mixer for 5 minutes with microcrystalline cellulose and sodium starch glycolate. The resultant mixture was then moistened for 5 minutes with a solution of polyvinylpyrrolidone in isopropanol and dried. The granulate was milled through a 1.0 mm sieve and lubricated for 2 min with magnesium stearate.

The granulate was compressed to tablets on a tabletting machine fitted with 12 mm punches. Each tablet contained an amount of sodium amoxicyllin corresponding to 200 mg amoxycillin.

The obtained tablets are covered with a separating layer and an enteric coating layer.

Solution for separating layer (for 10 kg tablets)

Hydroxypropyl methylcellulose 300 g
Hydrogen peroxide (30%) 0.003 g
Water purified 2700 g

Solution for enteric coating layer (for 10 kg tablets)

Methacrylic acid copolymer dispersion (30%) 2450 g
Polyethylene glycol 400 80 g
Titanium dioxide 100 g
Water purified 1960 g

Claims

1. An enteric coated oral dosage form comprising sodium amoxycillin.

2. A dosage form as claimed in claim 1, characterised in that the dosage form is a single unit tableted dosage form.

3. A dosage form as claimed in claim 1, characterised in that the dosage form is a multiple unit tableted dosage form.

4. A dosage form according to claim 3, characterised in that the dosage form comprises individually enteric coated pellets comprising sodium amoxycillin, and the enteric coated pellets and tablet excipients are compressed into a tablet.

5. A dosage form as claimed in any one of claims 1 to 4, characterised in that the sodium amoxycillin is amorphous.

6. A dosage form as claimed in any one of claims 1 to 5 in combination with a dosage form comprising a proton pump inhibitor.

7. A dosage form as claimed in any one of claims 1 to 5 which further comprises a proton pump inhibitor.

8. A dosage from as claimed in claim 7, characterised in that the proton pump inhibitor is omeprazole, S-omeprazole or an alkaline salt thereof.

9. The use of sodium amoxycillin in the manufacture of an enteric coated oral dosage form.

10. A process for the manufacture of an enteric coated single unit dosage form comprising sodium amoxycillin, characterised in that sodium amoxycillin is mixed with tablet

excipients, compressed into a tablet and the tablet is coating layered with an enteric coating.

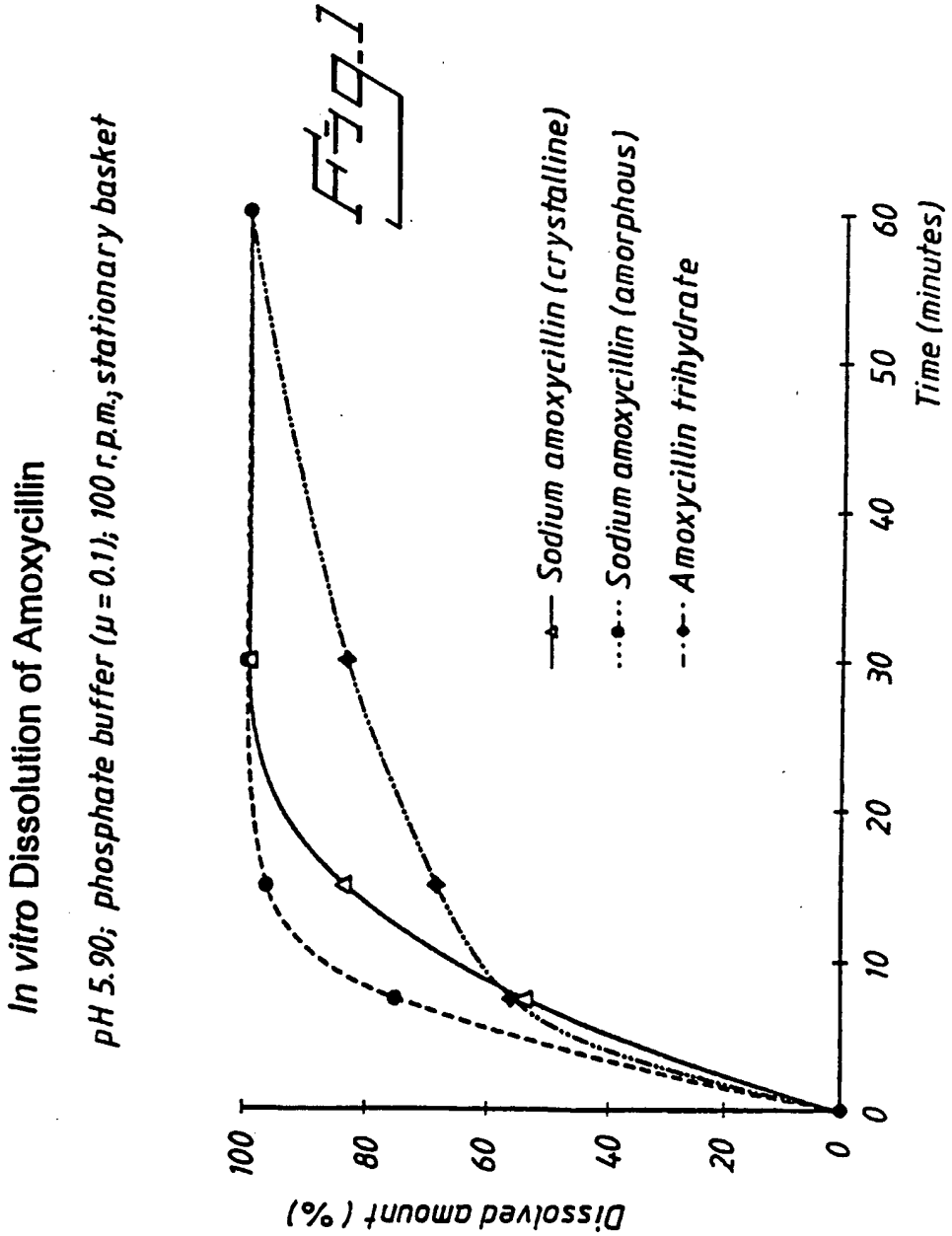
11. A process for the manufacture of an enteric coated oral dosage form comprising a multiplicity of enteric coated pellets of sodium amoxycillin, characterised in that sodium amoxycillin is mixed with pharmaceutically acceptable excipients, the mixture is formulated into pellets, the pellets are coating layered with an enteric coating, the coated pellets mixed with tablet excipients and compressed into a tablet.

12. A process according to any one of claims 10 and 11, characterised in that the prepared tablets or pellets comprising sodium amoxycillin are coating layered with a separating layer before application of the enteric coating layer.

13. The use of sodium amoxycillin in the manufacture of an enteric coated oral dosage form for use in the treatment of *Helicobacter pylori* infections.

14. A method for the treatment of *Helicobacter pylori* infections in mammals and man by administration to a host in need thereof a therapeutically effective dose of an enteric coated oral dosage for according to any one of claims 1 to 8.

Fig. 1


In vitro Dissolution of Amoxycillin
pH 5.90; phosphate buffer (μ = 0.1); 100 r.p.m; stationary basket
Sodium amoxycillin (crystalline)
Sodium amoxycillin (amorphous)
Amoxycillin trihydrate
Dissolved amount (%)
Time (minutes)
0
20
40
60
80
100
0
10
20
30
40
50
60

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00356

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/28, A61K 9/52, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, EMBASE, MEDLINE, WPI, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9702020 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 January 1997 (23.01.97), page 3, line 7 - page 7, line 26, claims --	1-14
X	WO 9525516 A1 (SMITHKLINE BEECHAM PLC), 28 Sept 1995 (28.09.95), page 3, line 24 - page 4, line 36, example 1, claims --	1-14
A	WO 9400112 A1 (AKTIEBOLAGET ASTRA), 6 January 1994 (06.01.94), page 4, line 20 - line 29, example 1, claims -- --------	1-14

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1998	01 -07- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00356

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claim 14 is directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.
PCT/SE 98/00356

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		EP 0841903 A	20/05/98
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